1: Am J Med Genet. 2004 Dec 15;131A(3):287-98.

Mechanistic and epidemiologic considerations in the evaluation of adverse birth outcomes following gestational exposure to statins.

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The cholesterol-lowering "statin" drugs are contraindicated in pregnancy, but few data exist on their safety in human gestation. We reviewed case reports for patterns suggesting drug-related effects on prenatal development and considered a variety of mechanisms by which such effects, if confirmed, might occur. This uncontrolled case series included all FDA reports of statin exposures during gestation, as well as others from the literature and from manufacturers. Exposures and outcomes were reviewed and were tabulated by individual drug. Age-specific rates of exposure to each drug among women of child-bearing age were estimated. Of 214 ascertained pregnancy exposures, 70 evaluable reports remained after excluding uninformative cases. Among 31 adverse outcomes were 22 cases with structural defects, 4 cases of intrauterine growth restriction, and 5 cases of fetal demise. There were two principal categories of recurrent

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structural defects: cerivastatin and lovastatin were associated with four reports of severe midline CNS defects; simvastatin, lovastatin, and atorvastatin were all associated with reports of limb deficiencies, including two similar complex lower limb defects reported following simvastatin exposure. There were also two cases of VACTERL association among the limb deficiency cases. All adverse outcomes were reported following exposure to cerivastatin, simvastatin, lovastatin, or atorvastatin, which are lipophilic and equilibrate between maternal and embryonic compartments. None were reported following exposure to pravastatin, which is minimally present in the embryo. Statins reaching the embryo may down-regulate biosynthesis of cholesterol as well as many important metabolic intermediates, and may have secondary effects on sterol-dependent morphogens such as Sonic Hedgehog. The reported cases display patterns consistent with dysfunction of cholesterol biosynthesis and Sonic Hedgehog activity. Controlled studies are needed to investigate the teratogenicity of individual drugs in this class.

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